



Doobary, S., & Lennox, A. J. J. (2020). Alkene Vicinal Difluorination: From Fluorine Gas to More Favoured Conditions. *SYNLETT*.
<https://doi.org/10.1055/s-0040-1707143>

Peer reviewed version

Link to published version (if available):
[10.1055/s-0040-1707143](https://doi.org/10.1055/s-0040-1707143)

[Link to publication record in Explore Bristol Research](#)
PDF-document

This is the author accepted manuscript (AAM). The final published version (version of record) is available online via Thieme Publishing at <https://www.thieme-connect.com/products/ejournals/pdf/10.1055/s-0040-1707143.pdf>. Please refer to any applicable terms of use of the publisher.

University of Bristol - Explore Bristol Research

General rights

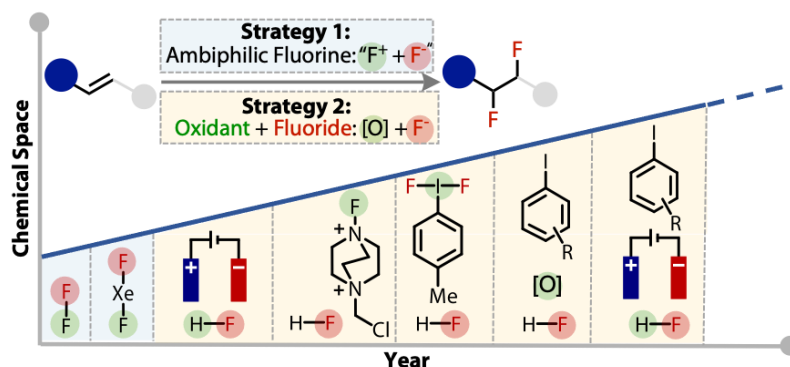
This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available:
<http://www.bristol.ac.uk/red/research-policy/pure/user-guides/ebr-terms/>

Alkene Vicinal Difluorination: From Fluorine gas to more Favoured conditions

Sayad Doobary
Alastair J. J. Lennox*

University of Bristol, School of Chemistry, Cantock's
Close, Bristol, BS8 1TS

a.lennox@bristol.ac.uk



Received:
Accepted:
Published online:
DOI:

Abstract Vicinal difluorinated alkanes are a medicinal chemistry-relevant moiety and are accessed via the difluorination of alkenes. This reaction has advanced from the use of highly reactive and unsafe reagents, which provide lower functional group tolerance and selectivity, to the use of safer and selective reagents that facilitate access to a broader scope of substrates. In this review article, we describe the details of these developments.

1. Introduction
2. Strategy 1: Ambiphilic fluorine sources
3. Strategy 2: Oxidant and Fluoride
4. Conclusions and Outlook

Key words Fluorination, Alkenes, Oxidation, Hyper valent iodine, Electrochemistry, Difluorination

1. Introduction

The presence of fluorine in active pharmaceutical ingredients has risen to over 30% in the 100 best-selling small-molecule drugs.¹ The replacement of a C–H bond with a highly polarised C–F bond can increase potency and improve pharmacokinetic properties.^{2,3} The electronegativity of fluorine and the strength of the C–F bond resists oxidative decomposition under physiological conditions and improves metabolic stability and lipophilicity.⁴ Fluorine reduces the basicity of neighbouring amines,⁵ which can also affect bioactivity.

The vicinal difluoroalkane unit has garnered recent academic attention, because it is a bioisostere for trifluoromethyl and ethyl groups,^{6–8} it has a high density of C(sp³)-F bonds, and has a unique propensity to adopt a gauche conformation in solution.^{9–13} Exploitation of this stereoelectronic effect is an emerging strategy for molecular design^{14,15} and has found application in organocatalysis^{16–18} and peptide mimics.^{19–21} The electronegativity of the fluorine atom lowers the energy of

the anti-bonding orbital σ^*_{C-F} such that it can partake in valuable energy lowering interactions. This is akin to other hyperconjugative interactions, such as the anomeric effect, whereby electronegative substituents on the anomeric position of a tetrahydropyran ring favour the axial position, due to favourable overlap between the lone pair on the oxygen and σ^*_{C-OMe} (**Figure 1A**). Similarly, in vicinal difluoroalkanes, orbital overlap between the adjacent σ_{C-H} orbital to σ^*_{C-F} creates a stabilising interaction as they adopt an antiperiplanar configuration (**Figure 1B**). There are two such interactions within these moieties and the outcome is that a gauche configuration between the two fluorine atoms is formed, and is worth around 1 kcal/mol in the case of difluoroethane.²² The conformational control of this functional moiety in the solution phase poses a potentially powerful tool to add to the medicinal chemist's toolkit.

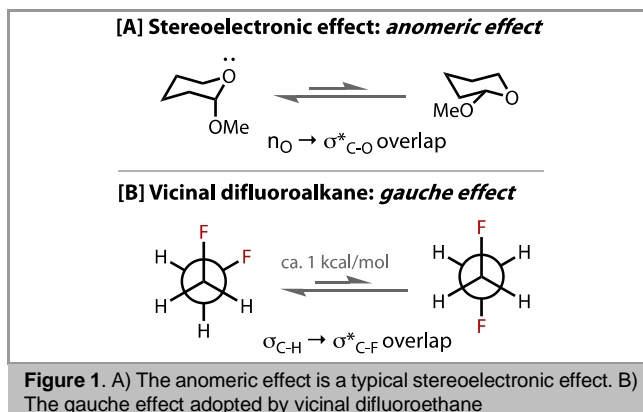


Figure 1. A) The anomeric effect is a typical stereoelectronic effect. B) The gauche effect adopted by vicinal difluoroethane

These functional groups are accessed by the difluorination of alkenes. In this article, we will discuss this transformation by describing the synthetic advances that have been made from the very early efforts to the current state-of-the-art.

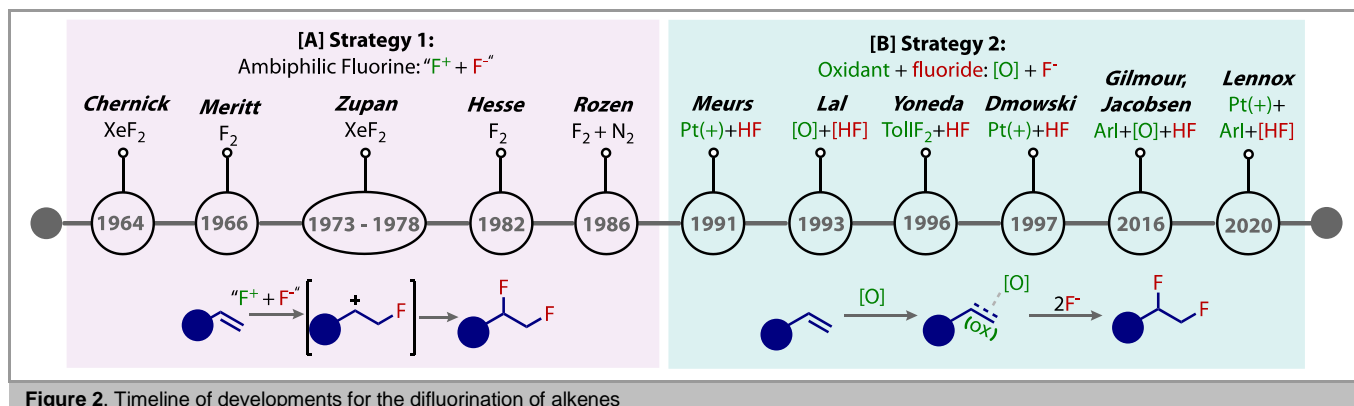


Figure 2. Timeline of developments for the difluorination of alkenes

There are two strategies to access this functional group from alkenes. The first is the use of an ambiphilic source of fluorine, which formally contains both F^+ and F^- equivalents and thus the necessary oxidising equivalents are self-contained in the reagent (**Figure 2A**). This approach was pioneered in the 1960s and 1970s. The second strategy combines a milder oxidant with a nucleophilic source of fluoride (**Figure 2B**), effectively separating out the oxidising equivalents from the reactive ambiphilic fluorine reagents. As the conditions are milder, this strategy improves chemoselectivity and safety. Current state-of-the-art methods focus on the *in situ* formation of hypervalent iodine oxidants in the presence of HF to difluorinate alkenes. These methods have successfully expanded this transformation into important and useful new areas of chemical space

2. Strategy 1: Ambiphilic Fluorine Sources

Early attempts at alkene difluorination were carried out using fluorine gas. In 1966, Merritt used this gas to difluorinate two activated, disubstituted styrenes, indene and acenaphthylene, in 43% and 11% yields, respectively (**Figure 3A**).²³ The authors observed major, uncharacterised fluorinated side-products. This approach was later expanded by Hesse to include α,β -unsaturated ketone **1** as part of steroidal structures (**Figure 3B**).^{24,25} Selectivity for an electron-deficient alkene was achieved in the presence of a more electron-rich alkene, however, only one example was demonstrated. In order to tame the reactivity of the reagent, Rozen diluted fluorine gas in nitrogen to slow its reaction, and also employed ethanol as the solvent, which hydrogen bonds to the fluorine and reduces its radical character (**Figure 3C**).²⁶ This was highlighted by the important observation that, without the alcohol solvent, the reaction yielded many unidentified fluorine signals, characteristic of non-discriminatory fluorine radical attack on the organic compound. Even though the reactivity of fluorine gas was dampened under these conditions, some unactivated substrates, such as cyclododecene (to make **2**) were still readily difluorinated. Rozen has also shown this system can be used for the selective difluorination of flavones in good yields (**Figure 3C**).²⁷

Academic interest with fluorine gas has more recently shifted toward the use of new micro-reactors that efficiently mix gas and liquid phases, allowing the use of less concentrated fluorine gas mixtures and overall safer systems.²⁸ However, the hazardous and expensive nature of fluorine gas renders widespread adoption of these approaches unlikely.

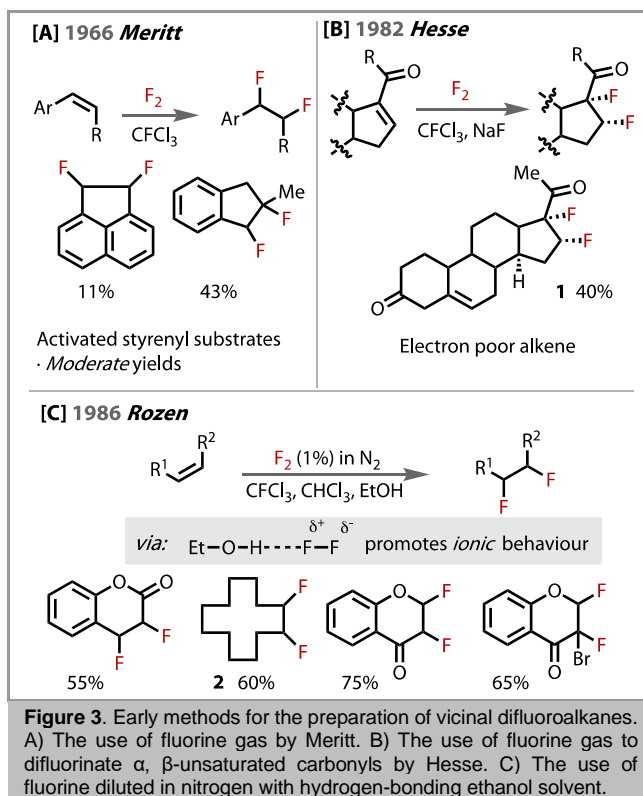
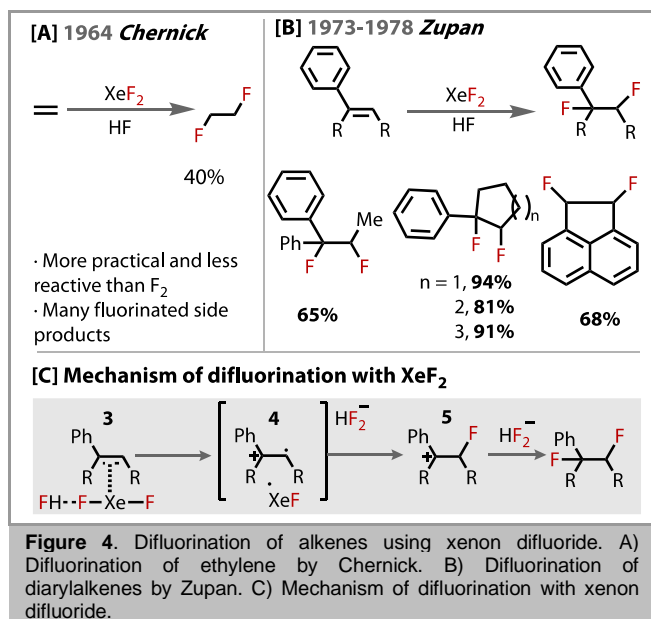


Figure 3. Early methods for the preparation of vicinal difluoroalkanes. A) The use of fluorine gas by Merritt. B) The use of fluorine gas to difluorinate α,β -unsaturated carbonyls by Hesse. C) The use of fluorine diluted in nitrogen with hydrogen-bonding ethanol solvent.

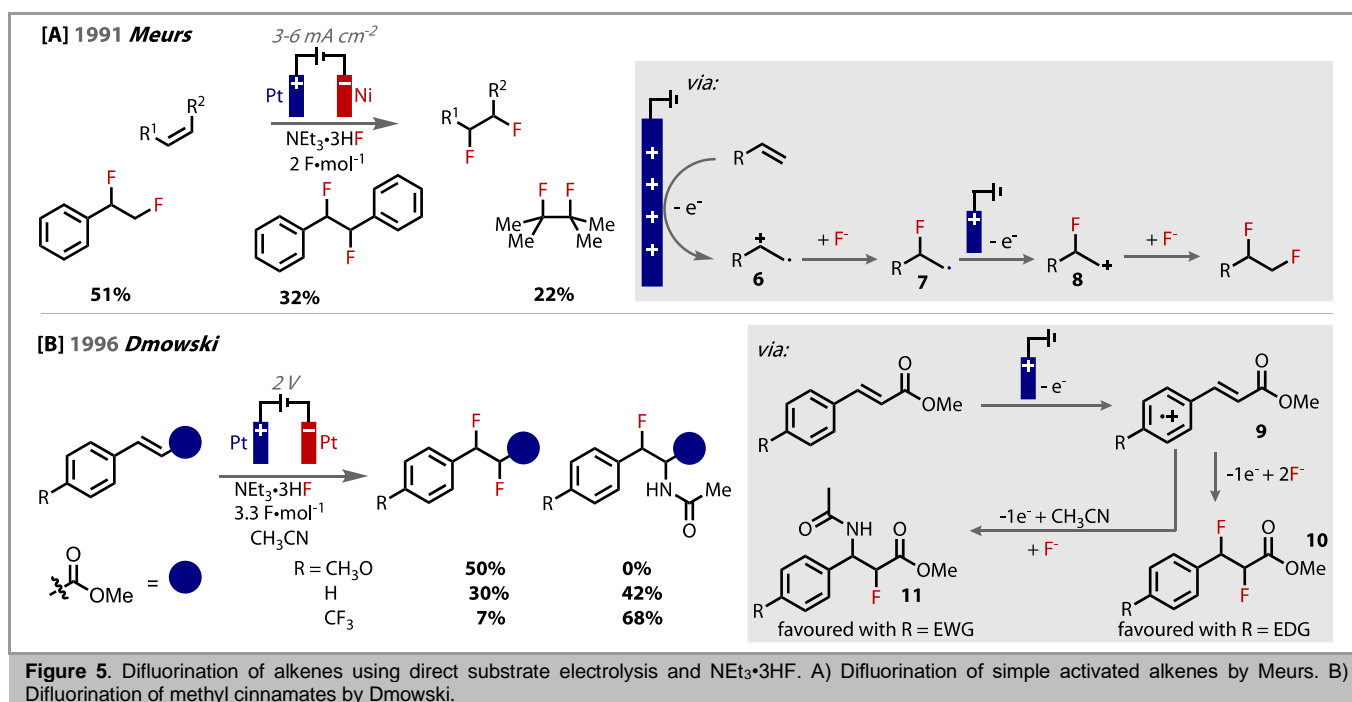
Alternative approaches at controlling the reactivity of fluorine gas were probed by using xenon difluoride.²⁹ Initially reported by Chernick, ethylene was difluorinated to produce *vic*-difluoroethane along with a majority of uncharacterisable fluorinated products (**Figure 4A**).³⁰ Zupan then produced a series of works detailing the reactivity of xenon difluoride with activated styrenyl alkenes. The substrates include diphenylalkenes,³¹ di-substituted³² and internal styrenes,³³ and 1-phenyl cycloalkenes.³⁴ (**Figure 4B**). Zupan postulated that a single electron transfer occurs between the oxidant and alkene (**3**) forming radical cation intermediate **4** (**Figure 4C**). Fluorine atom addition from xenon fluoride radical produces the fluorinated carbocation **5**, which is trapped by fluoride. However, as with fluorine gas, the reactive nature of this electrophilic fluorine source makes it a less than ideal reagent for widespread use.



3. Strategy 2: Oxidant and Fluoride

To improve the functional group tolerance and increase the number of alkene types that are amenable to the reaction, greater control and selectivity is achieved by employing a separate oxidant and a nucleophilic fluoride source. These reagents are more practical and safer to handle, a milder oxidising environment is created, and the reagents are less expensive.

The first to adopt this approach was Meurs in 1991, who explored the use of electrochemical oxidation to difluorinate alkenes (**Figure 5A**).³⁵ Activated alkenes were oxidised directly on the anode surface to produce the radical cation **6**. After fluorination to produce neutral radical **7**, a further oxidation and fluorination cycle gives product **8**. A significant advantage of this approach is the ability to apply the exact potential required for oxidation of a substrate in order to avoid over-oxidation, which readily occurs upon application of an excess oxidising potential. Protons are reduced on the cathode to produce hydrogen gas and are therefore the sacrificial oxidant. Meurs showed that by using a solution of triethylamine tris (hydrogen fluoride) ($NEt_3 \cdot 3HF$) and a platinum anode styrene, trans-stilbene and 2,3-dimethyl 2-butene were difluorinated in moderate yields. However, due to the unstable nature of the reactive species formed after oxidation, a mixture of products was often observed. Dmowski, on the other hand, achieved good chemoselectivity in the difluorination of methyl cinnamates (**Figure 5B**).³⁶ Direct oxidation of the cinnamate produced radical cation **9**, forming either the difluorination product **10** or the Ritter amide product **11** following nucleophilic addition of acetonitrile. Interestingly, the more electron donating groups on the ring led to increased amounts of the difluorination product and more electron withdrawing groups gave more Ritter amidation products.



Lal was the first to combine an oxidant with fluoride (**Figure 6**).³⁷ Employing the electrophilic fluorine source, Selectfluor, and pyridinium poly(hydrogen fluoride) (Py•9HF), difluorination of α -methylstyrene and trans-stilbene was achieved in 66% and 65% yields, respectively. Unfortunately, reaction of unactivated alkenes were unsuccessful, such as the formation of difluorocyclododecene **12**, which is likely due to insufficient stabilisation of the resulting carbocation. Without stabilisation from an aromatic ring the reaction did not proceed, thus significantly limiting the scope of these conditions.

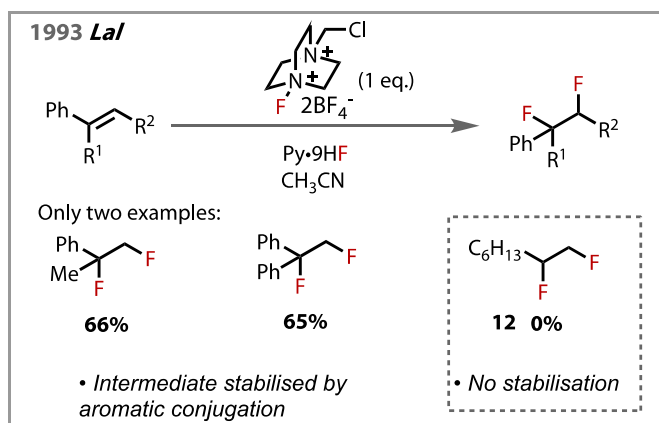


Figure 6. Difluorination of alkenes using Selectfluor and Py•9HF.

The reaction conditions described thus far work well on activated substrates but are less proficient in accessing vicinal difluorides from unactivated alkenes. To address this issue, Yoneda tested the use of *p*-tolylidifluoro- λ^3 -iodane (**13**) as a stoichiometric oxidant with triethylamine penta(hydrogen fluoride) (NEt₃•5HF) in CH₂Cl₂ at -78 °C (**Figure 7**).³⁸ λ^3 -Iodane **13** is a hypervalent iodine reagent that is both an I(III) oxidant and a fluoride source.^{39–41} Using this reagent, Yoneda was able to transform a small number of unactivated alkenes, such as long-chain terminal alkenes, **14** and **15**, and cyclohexene **16**, into their corresponding difluorinated products. Tolerance of alkyl chloride and ester functionality was also demonstrated. Yoneda's proposed mechanism starts with the formation of iodonium **17**. Evidence for a nucleophilic attack from the alkene was attained from the observation that the terminal alkene reacted preferentially to the electron poor enone in substrate **15**. The first fluoride addition forms iodane **18**, which then undergoes a second fluoride addition to form the difluorinated product. This mechanism is consistent with the *syn*-selectivity observed in cyclohexenyl product **16**. Yoneda's proposed mechanism also includes the necessary activation of iodane **13**. In this case, a Brønsted acid activation from hydrofluoric acid (HF) is suggested.

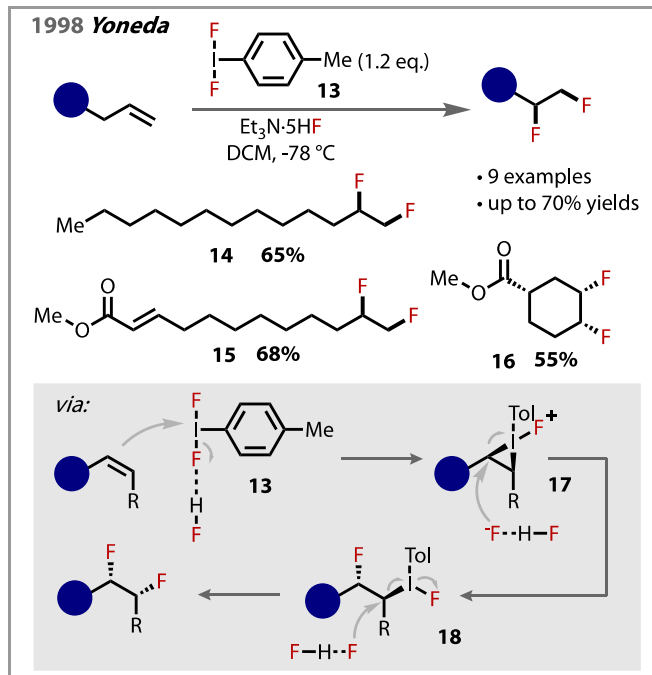


Figure 7. Difluorination of alkenes using *p*-tolylidifluoro- λ^3 -iodane (**13**) and Et₃N•5HF.

Difluorinated hypervalent iodine reagents were first synthesised from the corresponding chloride-substituted derivative. For example, in 1966, Carpenter prepared phenyldifluoro- λ^3 -iodane **19** from phenyldichloro- λ^3 -iodane in the presence of mercuric oxide and aqueous HF (**Figure 8A**).⁴² Wishing to avoid the toxic nature of mercuric oxide, Hara explored a safer alternative and reported a three step route from the aryl iodide (**Figure 8B**).⁴³ Chlorine gas was used to oxidise up to iodine(III), followed by hydrolysis to form the iodoso benzene and fluorination with aqueous HF. This process was tested on four different iodoarenes and gave good overall yields. Shreeve reported a more direct, one-step process from the iodoarene, using Selectfluor as the oxidant and NEt₃•3HF as the nucleophilic source of fluoride (**Figure 8C**).⁴⁴ The method was broadly applicable to electron-rich aryl iodides. These studies were further developed by Gilmour, who in 2017 reported HF-free conditions for the synthesis of aryl difluoro- λ^3 -iodanes, using caesium fluoride and Selectfluor (**Figure 8D**).⁴⁵ The fact that HF is not required for this reaction renders these conditions the current procedure of choice.

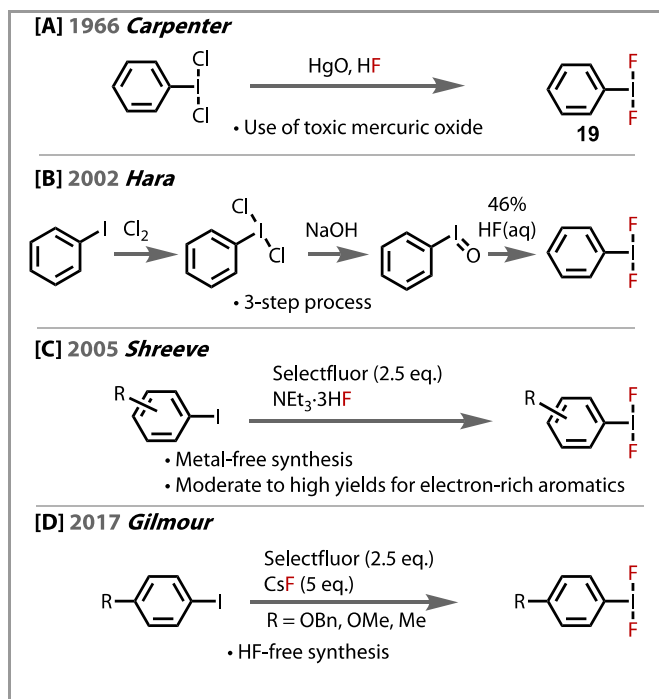


Figure 8. Synthesis of hypervalent iodine reagents from their corresponding aryl iodides. A) HgO and HF by Carpenter; B) Mercury-free synthesis from Hara; C) Selectfluor and $\text{NEt}_3 \cdot 3\text{HF}$ by Shreeve; and D) Selectfluor and CsF from Gilmour.

Difluoro iodane reagents **13** or **19** are troublesome to store and use, due to light-, air- and temperature-sensitivity.^{44–46} Therefore, conditions for their *in situ* preparation for alkene difluorination would clearly be advantageous. This problem was solved in 2016, with simultaneous reports from Jacobsen and Gilmour, who developed reaction conditions to generate aryl difluoro- λ^3 -iodanes *in situ* for alkene difluorination.^{47,48} In both of their systems, they implemented a combination of aryl iodide, external oxidant and an HF source. The *in situ* generation of hypervalent iodine enables the aryl iodide to play a catalytic role in the mechanism and sub-stoichiometric quantities are employed.

The optimised conditions for Gilmour's difluorination system take inspiration from those of Shreeve to form *p*-tolyl difluoro- λ^3 -iodane (**13**), which include the combination of Selectfluor and an HF source.⁴⁷ Forming **13** in this way in the presence of terminal alkenes successfully led to the desired fluorinated products. The use of either $\text{NEt}_3 \cdot 3\text{HF}$ or $\text{py} \cdot 9\text{HF}$ led to low yields, however, they found that a mixture of the two gave improved yields with 4.5 HF:amine (amine: pyridine + triethylamine) giving the best results. Terminal alkenes worked well in the reaction (**Figure 9A**) with tolerance to several functionalities, including esters (**20**), ethers (**21**) and α - β unsaturated ketones. Electron-poor benzylic ethers bearing, for example, pentafluoro (**22**) or nitro groups, required a higher HF:amine ratio. In depth NMR studies suggested that cationic iodane **23** is an intermediate in the mechanism (**Figure 9B**),⁴⁵ which supports the proposed oxidative delivery of fluorine to iodine from Selectfluor. With **13** formed, the rest of the proposed mechanism followed that of Yoneda's with stoichiometric use of **13**.³⁸

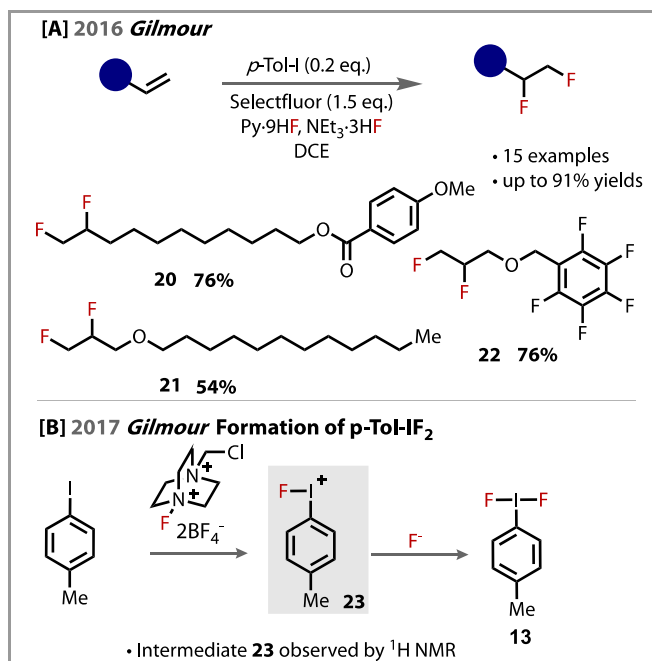
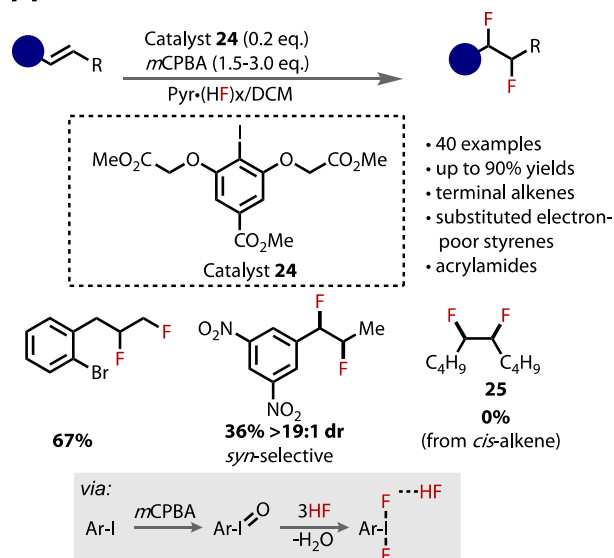


Figure 9. A) Difluorination of alkenes using *p*-tolyl iodide, Selectfluor and HF:amine. B) Evidence for the monofluorinated iodane intermediate.

Jacobsen optimised a difluorination system that utilised aryl iodide catalyst **24**, which was found to be more efficient than **13** and is more amenable to the incorporation of chirality (**Figure 10A**).⁴⁸ The optimised conditions included the use of *m*CPBA and $\text{Py} \cdot 9\text{HF}$, and was amenable to terminal alkenes and styrenyl substrates containing heterocycles and electron-poor rings. It was noted that the reaction lacked tolerance of *cis*-alkenes, as the attempted reaction of *E*-5-decene **25** led to mixtures of unidentified fluorinated and oligomeric products. Slow addition of alkene was also required to avoid competing epoxidation with *m*CPBA. The postulated mechanism includes the initial formation of iodosoarene upon the action of *m*CPBA on aryl iodide. Fluorination of this reagent then occurs, a transformation previously established by Hara⁴³ and Wirth,⁴⁹ and alkene difluorination then ensues. High syn-diastereoselectivity was observed in the substituted styrenyl substrates, which is readily explained by the stereospecific double fluoride displacement mechanism proposed. However, interestingly, *anti*-diastereoselectivity was observed with a number of substrates, including 2-nitro styrenes and acrylamides (**Figure 10B**). This was proposed to be due to anchimeric assistance through the displacement of iodine by the neighbouring oxygen, either from a nitro group or amide to form intermediates **26** or **27**, respectively. Double displacement at this position leads to a retention of configuration and overall *anti*-difluorination. A range of acrylamides were explored, which also demonstrated tolerance of substrates lacking carbocation-stabilising functionalities in the β -position.

[A] 2016 Jacobsen



[B] Anti-difluorination: anchimeric assistance pathway

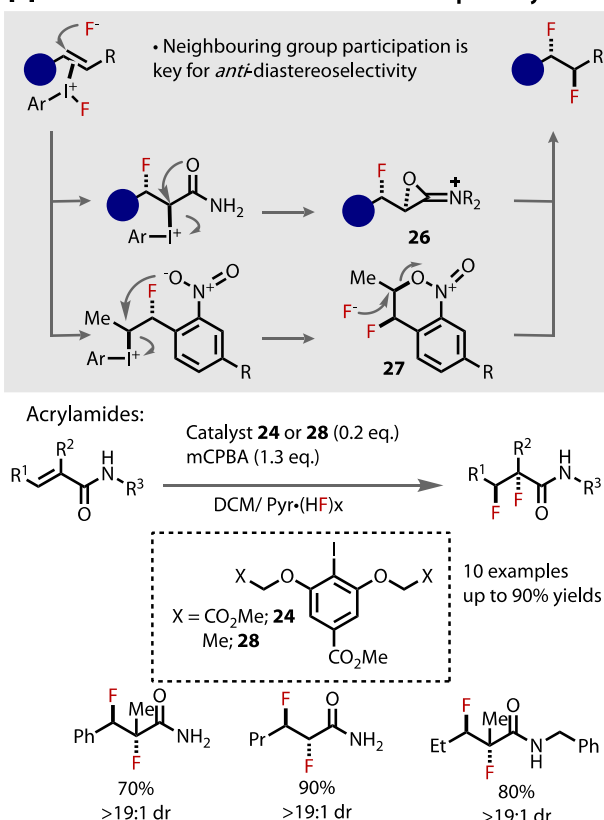
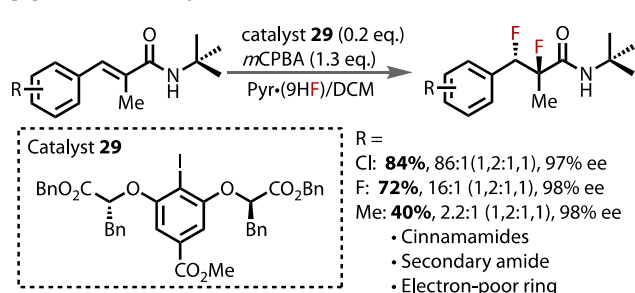


Figure 10. A) Difluorination of alkenes using aryl iodide, $m\text{CPBA}$ and $\text{Py}\cdot 9\text{HF}$ by Jacobsen; B) Anchimeric assistance pathway leads to *anti*-difluorination of *trans*-alkenes.

Jacobsen followed up these findings by developing an enantioselective difluorination of substituted cinnamamides. By taking advantage of amide anchimeric assistance and chiral aryl iodide catalyst **29**, several substrates were demonstrated in the reaction with $m\text{CPBA}$ and $\text{py}\cdot 9\text{HF}$ (**Figure 11A**).⁵⁰ The scope of amenable substrates was tight, due to a problematic 1,1-difluorination side reaction. This rendered substitution alpha to the carbonyl necessary, as well as a bulky secondary amide, and electron-withdrawing substituents on the arene ring. For example, substrates containing 4-fluoro or 4-chloro

rings produced the 1,2-difluoride, whereas more electron-rich substitution, such as 4-methyl, led to poorer selectivity due to competing 1,1-difluorination. These observations with more reactive rings are consistent with the intermediate formation of a phenonium ion (**30**) for the 1,1-difluorination (**Figure 11B**). Decreasing the reactivity of the ring with electron-withdrawing substitution thus favours participation of the amide, which forms iminium ion **31** leading to 1,2-difluorination.

[A] 2019 Jacobsen, enantioselective difluorination



[B] 1,1- vs 1,2-difluorination

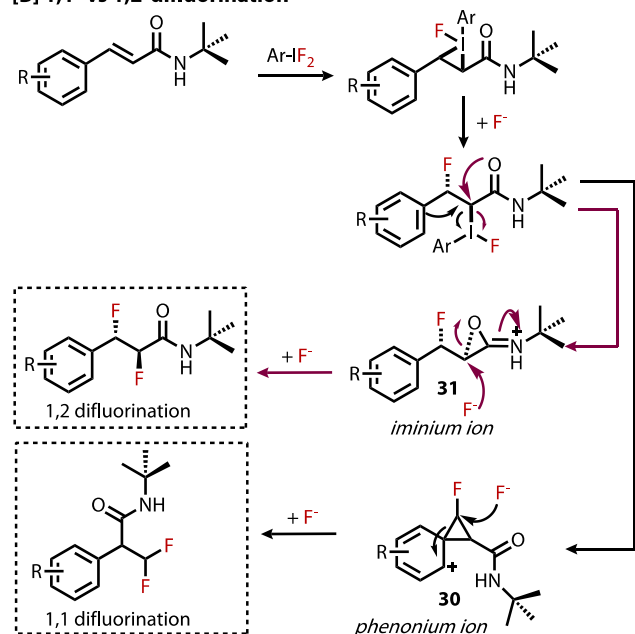


Figure 11. A) Enantioselective difluorination of cinnamamides using aryl iodide, $m\text{CPBA}$ and $\text{Py}\cdot 9\text{HF}$, ratios of 1,2- to 1,1-difluorinated products. B) Two pathways that lead to the 1,1- and 1,2-difluorination products.

The 1,1-difluorination of alkenes via a phenonium ion has been previously studied,⁵¹⁻⁵³ most notably by Szabo⁵⁴ and then again by Jacobsen,⁵⁵ who employed a chiral iodoarene to transform styrenes into gem 1,1-difluorinated products with moderate to very good enantioselectivity and yields. Gilmour and co-workers applied their vicinal difluorination conditions to styrenyl substrates (**Figure 12**) with the use of chiral catalyst **32**.⁵⁶ The ratio of HF to amine ($\text{Py} + \text{NEt}_3$) was found to impact the selectivity of 1,1- to 1,2-difluorination: 9HF:amine gave *gem*-difluorination, but 4.5HF:amine gave the vicinal product. These latter conditions showed good 1,2 selectivity for a range of substrates containing electron-withdrawing groups, such as nitro, sulfones and trifluoromethyl. However, without electron-poor, deactivating substituents on the ring, 1,1-difluorination was favoured, which limits the scope. The enantioselectivity of

the products from the reaction were moderate to good but were improved to excellent on recrystallisation of the product.

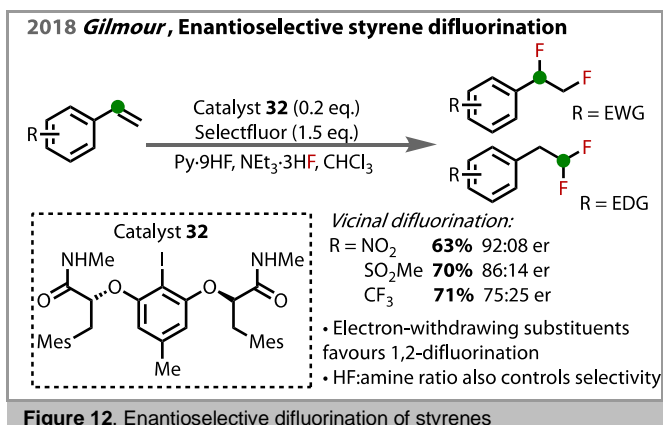


Figure 12. Enantioselective difluorination of styrenes

While the advances made in alkene vicinal difluorination were substantial, (achieving milder conditions, using more readily-available, safer reagents and introducing enantioselectivity to certain substrate classes) a number of problems remained. For example, substrates that contain electron-rich functionality were not amenable to the protocols developed and substituted alkenes were also not well represented. In addition, the use of stoichiometric quantities of oxidants with safety, cost and sustainability concerns, rendered these protocols less attractive to scale-up. With these considerations in mind, our group hypothesised that the use of electrochemical oxidation could ameliorate these problems. The advantage of an electrochemical approach is the unique ability to temporally and spatially separate the redox events and to precisely select the oxidation potential. These features can facilitate the circumvention of unwanted side-reactions, improve functional group tolerance and sustainability. The heterogenous nature of an electrochemical set-up also primes it for scale up. We proposed that, by controlling the rate and location of the unstable hypervalent iodine oxidant, we should be able to overcome the challenges identified, and, by reducing protons on the cathode to generate hydrogen gas, a more sustainable process could be achieved (**Figure 13**). In early 2020, we reported the successful realisation of such a protocol,⁵⁷ which provided access to the elusive chemical space of electron-rich substrates in a safe and more sustainable manner.

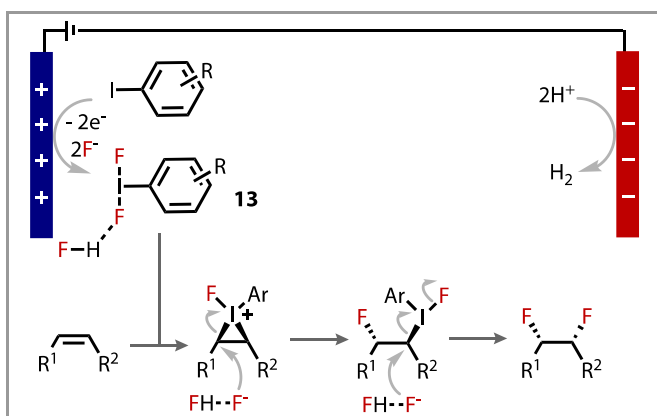


Figure 13. Mechanistic hypothesis for the electrochemical aryl iodide-mediated difluorination of alkenes.

The optimisation programme first considered the effect of aryl iodides of varying electronics on the difluorination of allylbenzene. Highly electron-rich and highly electron-poor iodoarenes both returned low yields. A fine balance of reactivity and instability was required and *p*-tolyl iodide gave the best results. The reaction was found to be highly sensitive to the pH, and a fine balance of HF:amine was required to achieve the optimal outcome. It was proposed that acidic HF is required to activate the iodane **13** toward reaction with alkene, but more acidic conditions reduces the activity of fluoride and thus attenuates the displacement of iodine. 5.6HF:amine was found to mark the “sweet-spot” of this balance. A solvent screen discovered that a mixture of HFIP and CH₂Cl₂ (3:7) produced an optimal yield. Cyclic voltammetry (CV) and NMR analysis revealed that the inclusion of HFIP, which has been exploited for other halogenation reactions,^{58–62} led to a milder oxidising environment and facilitated the formation of **13**. Utilisation of sub-stoichiometric quantities of *p*-tolyl iodide unfortunately led to lower yields, however, it was recovered after the reaction, thereby confirming its catalytic role.

With the optimised ‘in-cell’ method in hand, a variety of terminal alkenes were tested, and produced good to excellent yields of electron-poor substrates that are resistant to oxidation (**Figure 14**). Functionality that was tolerated included sulfonates, ethers, alcohols, heterocycles, aryl halides and esters. This system was readily scaled up to gram and decagram scales with little loss in yield. We also carried out the reaction with commercially available equipment with no loss in product yield.

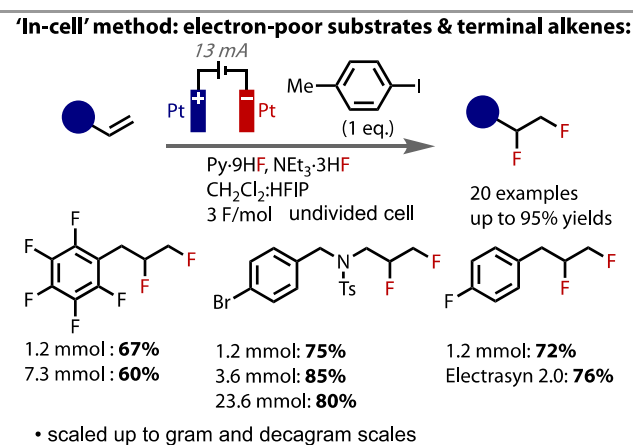


Figure 14 Electrochemical iodoarene-mediated difluorination of alkenes. “In-cell” method using an undivided cell for electron-poor substrates.

Encouraged by these results, electron-rich substrates were tested, but, unfortunately, were found to be incompatible with the reaction conditions in their current form. For example, 4-allyltoluene (a representative electron-rich substrate) decomposed and produced a low yield of product because it oxidises more readily than the required 4-tolyl iodide (**Figure 15**). This contrasts an electron-poor substrate, such as allylpentafluorobenzene, which showed no oxidative feature up to 1.9 V (vs Fc/Fc⁺). Thus an ‘ex-cell’ method was applied, whereby **13** was first prepared electrochemically, now in a divided cell to protect it from cathodic decomposition, and then alkene was added after electrolysis (**Figure 16**). This approach provided a significant increase in yield for electron-rich

substrates, including aniline, di- and trisubstituted alkenes, and morpholino compounds.

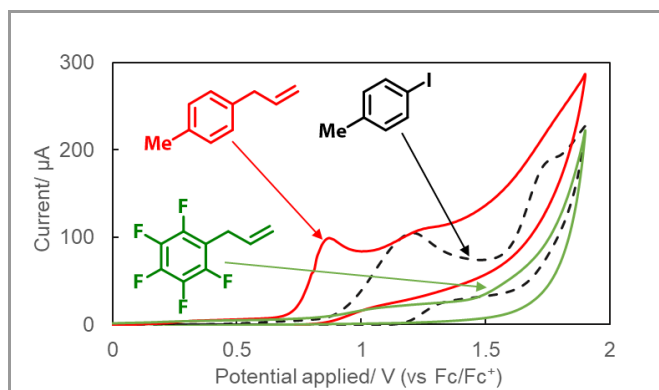


Figure 15. CVs of iodotoluene (5 mM, dashed, black line), 4-allyltoluene (5 mM, red line) and allylpentafluorobenzene (5 mM, green line) to this solution.

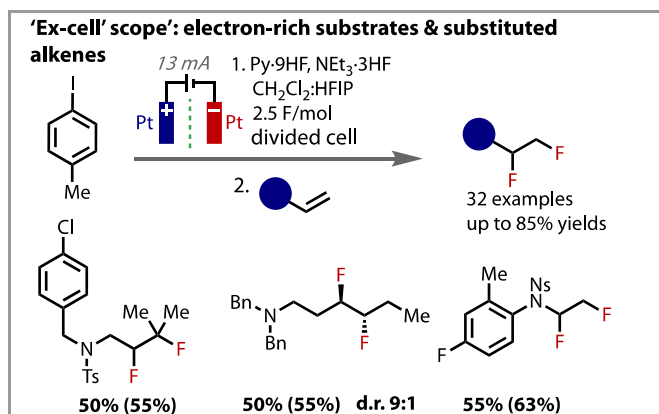


Figure 16. 'Ex-cell' method using a divided cell for electron-rich substrates. Yields in brackets refer to NMR yields.

The difluorination of several electron-rich substrates was compared against other methods recently reported (**Figure 17**).^{37,47,48} It was found that all the electron-rich substrates tested performed poorly under other reaction conditions, thus reflecting the importance of the electrochemical 'ex-cell' approach. The sustainability of these four methods were also compared, using an E-factor analysis (ratio of total waste to product), which showed that the electrochemical method was the least wasteful.

Comparison of reaction conditions:

Condition	Ar-I (1 eq.) + [HF]	Cyclic Ether	Complex Molecule
Electrochem			
Ar-I (1 eq.) + [HF]	85%	37%	58%
Selectfluor			
Ar-I (0.2 eq.) + [HF]	<5%	<5%	0%
mCPBA			
Ar-I (0.2 eq.) + [HF]	33%	15%	<5%
Selectfluor [HF]			
[HF]	0%	0%	<5%

Figure 17. Comparison of recent difluorination conditions.

4. Conclusions and Outlook

In this review article, we have detailed how the methods for oxidative difluorination of alkenes have developed. The systems have improved from the use of unsafe and unselective reagents, such as fluorine gas, to more sustainable and selective systems, such as electrochemistry. These new systems provide access to new chemical space in a scalable manner. Further advances are still necessary to fully realise the potential of this functional group in applications such as active pharmaceutical ingredients. These include an expansion of the scope of enantioselective difluorination, *anti*-diastereoselectivity, and without the use of corrosive HF sources. An HF-free protocol should facilitate access to acid-sensitive functionalities in a safer manner. Significant challenges exist to realising these ambitious yet important aspirations, which may be necessary for the incorporation of the vicinal difluoride unit into high value products.

Funding Information

We would like to thank the Royal Society (University Research Fellowship to A.J.J.L.), EPSRC (EP/G036764/1) and GSK for funding.

Acknowledgment

[Click here to insert acknowledgment text. Funding sources and grant numbers should be given above in the Funding Information section.](#)

References

- (1) McGrath, N. A.; Brichacek, M.; Njardarson, J. T. *J. Chem. Educ.* **2010**, *87*, 1348.
- (2) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. *J. Med. Chem.* **2015**, *58*, 8315.
- (3) Huchet, Q. A.; Trapp, N.; Kuhn, B.; Wagner, B.; Fischer, H.; Kratochwil, N. A.; Carreira, E. M.; Müller, K. J. *Fluor. Chem.* **2017**, *198*, 34.
- (4) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308.
- (5) Morgenthaler, M.; Schweizer, E.; Hoffmann-Röder, A.; Benini, F.; Martin, R. E.; Jaeschke, G.; Wagner, B.; Fischer, H.; Bendels, S.; Zimmerli, D.; Schneider, J.; Diederich, F.; Kansy, M.; Müller, K. *ChemMedChem* **2007**, *2*, 1100.
- (6) Molnár, I. G.; Thiehoff, C.; Holland, M. C.; Gilmour, R. *ACS Catal.* **2016**, *6*, 7167.
- (7) Erdeljac, N.; Kehr, G.; Ahlqvist, M.; Knerr, L.; Gilmour, R. *Chem. Commun.* **2018**, *54*, 12002.
- (8) Erdeljac, N.; Bussmann, K.; Schöler, A.; Hansen, F. K.; Gilmour, R. *ACS Med. Chem. Lett.* **2019**, *10*, 1336.
- (9) Wolfe, S. *Acc. Chem. Res.* **1972**, *5*, 102.
- (10) O'Hagan, D.; Rzepa, H. S.; Schüler, M.; Slawin, A. M. Z. *Beilstein J. Org. Chem.* **2006**, *2*, 19.
- (11) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308.
- (12) Thiehoff, C.; Rey, Y. P.; Gilmour, R. *Isr. J. Chem.* **2017**, *57*, 92.
- (13) Goodman, L.; Gu, H.; Pophristic, V. J. *Phys. Chem. A* **2005**, *109*, 1223.
- (14) Zimmer, L. E.; Sparr, C.; Gilmour, R. *Angew. Chemie - Int. Ed.* **2011**, *50*, 11860.
- (15) Bentler, P.; Erdeljac, N.; Bussmann, K.; Ahlqvist, M.;

- Knerr, L.; Bergander, K.; Daniliuc, C. G.; Gilmour, R. *Org. Lett.* **2019**, *21*, 7741.
- (16) Molnár, I. G.; Holland, M. C.; Daniliuc, C.; Houk, K. N.; Gilmour, R. *Synlett* **2016**, *27*, 1051.
- (17) Aufiero, M.; Gilmour, R. *Acc. Chem. Res.* **2018**, *51*, 1701.
- (18) Vega-Peñaloza, A.; Paria, S.; Bonchio, M.; Dell'Amico, L.; Companyó, X. *ACS Catal.* **2019**, *9*, 6058.
- (19) Schüller, M.; O'Hagan, D.; Slawin, A. M. Z. *Chem. Commun.* **2005**, 4324.
- (20) Yamamoto, I.; Jordan, M. J. T.; Gavande, N.; Doddareddy, M. R.; Chebib, M.; Hunter, L. *Chem. Commun.* **2012**, *48*, 829.
- (21) Hu, X.-G.; Thomas, D. S.; Griffith, R.; Hunter, L. *Angew. Chemie Int. Ed.* **2014**, *53*, 6176.
- (22) Buissonneaud, D. Y.; van Mourik, T.; O'Hagan, D. *Tetrahedron* **2010**, *66*, 2196.
- (23) Merritt, R. F.; Johnson, F. A. J. *Org. Chem.* **1966**, *31*, 1859.
- (24) Barton, D. H. R.; Lister-James, J.; Hesse, R. H.; Pechet, M. M.; Rozen, S. J. *Chem. Soc., Perkin Trans. 1* **1982**, 1105.
- (25) Alker, D.; Barton, D. H. R.; Hesse, R. H.; Lister-James, J.; Markwell, R. E.; Pechet, M. M.; Rozen, S.; Takeshita, T.; Toh, H. T. In *Reason and Imagination*; **1996**; 419.
- (26) Rozen, S.; Brand, M. J. *Org. Chem.* **1986**, *51*, 3607.
- (27) Vints, I.; Rozen, S. J. *Org. Chem.* **2014**, *79*, 7261.
- (28) de Mas, N.; Günther, A.; Schmidt, M. A.; Jensen, K. F. *Ind. Eng. Chem. Res.* **2009**, *48*, 1428.
- (29) Tius, M. A. *Tetrahedron* **1995**, *51*, 6605.
- (30) Shieh, T.-C.; Yang, N. C.; Chernick, C. L. J. *Am. Chem. Soc.* **1964**, *86*, 5021.
- (31) Zupan, M.; Pollak, A. J. *Chem. Soc. Chem. Commun.* **1973**, 845.
- (32) Zupan, M.; Pollak, A. J. *Org. Chem.* **1977**, *42*, 1559.
- (33) Šket, B.; Zupan, M. J. *Chem. Soc. Perkin Trans. 1* **1977**, 2169.
- (34) Zupan, M.; Sket, B. J. *Org. Chem.* **1978**, *43*, 696.
- (35) Meurs, J. H. H.; Eilenberg, W. *Tetrahedron* **1991**, *47*, 705.
- (36) Dmowski, W.; Kozłowski, T. *Electrochim. Acta* **1997**, *42*, 513.
- (37) Lal, G. S. J. *Org. Chem.* **1993**, *58*, 2791.
- (38) Sawaguchi, M.; Hara, S.; Yoneda, N. J. *Fluor. Chem.* **2000**, *105*, 313.
- (39) Lemal, D. M.; Tao, J.; Murphy, G. K. In *Encyclopedia of Reagents for Organic Synthesis*; John Wiley & Sons, Ltd, **2016**; 1.
- (40) Kohlhepp, S. V.; Gulder, T. 6270 | *Chem. Soc. Rev* **2016**, *45*, 6270.
- (41) Murphy, G. K.; Gulder, T. In *Fluorination*; Springer Singapore, **2018**; 1.
- (42) Carpenter, W. J. *Org. Chem.* **1966**, *31*, 2688.
- (43) Sawaguchi, M.; Ayuba, S.; Hara, S. *Synthesis (Stuttg.)* **2002**, *2002*, 1802.
- (44) Ye, C.; Twamley, B.; Shreeve, J. M. *Org. Lett.* **2005**, *7*, 3961.
- (45) Sarie, J. C.; Thiehoff, C.; Mudd, R. J.; Daniliuc, C. G.; Kehr, G.; Gilmour, R. J. *Org. Chem.* **2017**, *82*, 11792.
- (46) Sun, H.; Wang, B.; DiMagno, S. G. *Org. Lett.* **2008**, *10*, 4413.
- (47) Molnár, I. G.; Gilmour, R. J. *Am. Chem. Soc.* **2016**, *138*, 5004.
- (48) Banik, S. M.; Medley, J. W.; Jacobsen, E. N. J. *Am. Chem. Soc.* **2016**, *138*, 5000.
- (49) Arrica, M. A.; Wirth, T. *European J. Org. Chem.* **2005**, *2005*, 395.
- (50) Haj, M. K.; Banik, S. M.; Jacobsen, E. N. *Org. Lett.* **2019**, *21*, 4919.
- (51) Kitamura, T.; Muta, K.; Oyamada, J. J. *Org. Chem.* **2015**, *80*, 10431.
- (52) Kitamura, T.; Yoshida, K.; Mizuno, S.; Miyake, A.; Oyamada, J. J. *Org. Chem.* **2018**, *83*, 14853.
- (53) Zhao, Z.; Racicot, L.; Murphy, G. K. *Angew. Chemie - Int. Ed.* **2017**, *56*, 11620.
- (54) Ilchenko, N. O.; Tasch, B. O. A.; Szabó, K. J. *Angew. Chemie Int. Ed.* **2014**, *53*, 12897.
- (55) Banik, S. M.; Medley, J. W.; Jacobsen, E. N. *Science (80-)* **2016**, *353*, 51.
- (56) Scheidt, F.; Schäfer, M.; Sarie, J. C.; Daniliuc, C. G.; Molloy, J. J.; Gilmour, R. *Angew. Chemie Int. Ed.* **2018**, *57*, 16431.
- (57) Doobary, S.; Sedikides, A. T.; Caldora, H. P.; Poole, D. L.; Lennox, A. J. J. *Angew. Chemie Int. Ed.* **2020**, *59*, 1155.
- (58) Sarie, J. C.; Neufeld, J.; Daniliuc, C. G.; Gilmour, R. *ACS Catal.* **2019**, *9*, 7232.
- (59) Minhas, H. K.; Riley, W.; Stuart, A. M.; Urbonaite, M. *Org. Biomol. Chem.* **2018**, *16*, 7170.
- (60) Imada, Y.; Röckl, J. L.; Wiebe, A.; Gieshoff, T.; Schollmeyer, D.; Chiba, K.; Franke, R.; Waldvogel, S. R. *Angew. Chemie Int. Ed.* **2018**, *57*, 12136.
- (61) Elsler, B.; Wiebe, A.; Schollmeyer, D.; Dyballa, K. M.; Franke, R.; Waldvogel, S. R. *Chem. - A Eur. J.* **2015**, *21*, 12321.
- (62) Arnold, A. M.; Pöthig, A.; Drees, M.; Gulder, T. J. *Am. Chem. Soc.* **2018**, *140*, 4344.

Biosketches



Alastair Lennox is a graduate of Manchester University and completed his PhD under the supervision of Professor Guy Lloyd-Jones. Following postdoctoral research with Prof. Matthias Beller as an Alexander von Humboldt Fellow, and with Prof. Shannon Stahl at the University of Wisconsin-Madison, he joined the University of Bristol as a Royal Society University Research Fellow. His research group's interests include the development of new selective and sustainable electrochemical methodologies for pharmaceutical and agrochemical use.
